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## Optimization of image-guided radiotherapy (IGRT) for lung cancer

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# Chapter 1

**Introduction and outline of the thesis**

## EPIDEMIOLOGY

Lung cancer is one of the leading causes of cancer related morbidity and mortality globally. In the Netherlands, in 2006 more than 10.000 new cases and almost 9.500 deaths of lung cancer were reported (1). Lung cancer deaths are more common in men, but have begun to decline, while incidence rates continue to rise among women (2,3). Smoking is the most important risk factor for lung cancer, with more than 85% of cases arising in smokers and ex-smokers. Other risk factors include exposure to environmental and occupational carcinogens.

## TREATMENT STRATEGIES

Radiotherapy plays an important role in the treatment of lung cancer, either as a single treatment modality or in combination with surgery and/or chemotherapy. In stage I lung cancer, surgery is considered to be the treatment of choice (4). Recently, excellent local control has been reported using stereotactic radiotherapy (SRT) in patients who are unfit for surgery. As local control rates of more than 90% have been reported using SRT for small stage I tumor lesions (5), two prospective randomized trials comparing surgery with SRT in patients who are fit to undergo surgery, are now underway. However, the majority of patients present with locally-advanced or metastatic disease, in which the prognosis is still poor despite the use of aggressive treatment strategies. In locally-advanced disease, 5-year survival rates range from 10-35% (6). In patients with stage III lung cancer and a good performance status, concurrent chemoradiotherapy is recommended, as meta-analyses have shown this regimen to be superior to either sequential chemoradiotherapy or radiotherapy alone (7-9). Although the addition of surgery to concurrent chemoradiotherapy has been shown to increase the 3-year progression-free survival, no survival benefit was observed (10). However, it has been suggested that a subgroup of patients showing down-staging after chemoradiotherapy may benefit from surgery, but many questions regarding clinical outcomes and adverse effects are still unanswered and awaiting randomized trials (11,12). The high local recurrence rates after resection of N<sub>2</sub> disease (in patients treated with neo-adjuvant

chemotherapy), as well as the availability of 3D-conformal radiotherapy, has renewed interest in the role of post-operative radiotherapy (13).

## GOALS AND CHALLENGES IN RADIOTHERAPY

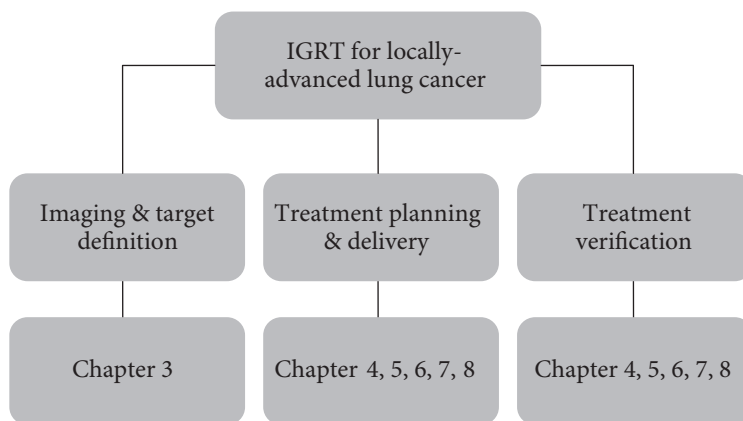
The primary goal of radiotherapy is to increase loco-regional control, while minimizing toxicity. Dose-escalation in locally-advanced disease results in a higher overall survival, but is also associated with an increased risk of damage to surrounding normal tissues (14). Ideally, the prescribed dose should be restricted to the tumor, without involving surrounding healthy tissue. However, this is difficult to accomplish because of uncertainties related to target definition, treatment planning and treatment delivery, but also because of technical limitations. Recent years have witnessed major technical advances, which enable improved accuracy of tumor targeting and also better avoidance of normal organs.

### Advances in target definition

Traditionally, target definition has been based on a 3-dimensional (3D) CT scan and involves contouring of the gross tumor volume (GTV), which is defined as clinically macroscopic disease. Safety margins are added in order to account for microscopic tumor extension (clinical target volume; CTV) and geometric inaccuracies, such as positional uncertainties or tumor motion (planning target volume; PTV) (15). The integration of functional imaging (i.e. 18-Fluoro-2-deoxy-glucose positron emission tomography; <sup>18</sup>FDG-PET) has been shown to significantly increase the accuracy of defining involved mediastinal nodes (16). Strategies to lower toxicity by reducing target volumes include: (i) the use of involved-field radiotherapy (IFRT), which only incorporates pathological nodes in the target volume, as opposed to the irradiation of clinically uninvolved mediastinal and supraclavicular nodes (17), (ii) the reduction of margins for PTV by accounting for setup inaccuracies and tumor motion for each individual patient. The latter is enabled by the use of patient-specific margins provided by 4-dimensional (4D) CT scans, which are respiration-correlated CT scans, permitting visualization of both spatial and temporal changes of the internal anatomy (18,19).

## Advances in treatment planning & delivery

Another strategy to increase the therapeutic ratio includes the generation of more conformal dose distributions. Examples of such approaches include intensity modulated radiotherapy (IMRT) and stereotactic radiotherapy. In addition, the development of motion management strategies allows for the use of smaller treatment fields. Lung tumor motion has been reported to range up to more than 30mm with 40% and 10% exceeding 5mm and 10mm, respectively (20,21). Examples of motion management techniques include: (i) use of a slow CT or 4DCT scan (ii) active breathing control (ABC) or deep-inspiration breath-hold (DIBH), where attempts are made to control tumor motion by actively or passively influence respiration-induced movements, (iii) respiration-gated radiotherapy (RGRT), where the tumor is irradiated in a pre-selected cycle of the respiratory phase during which motion is relatively limited (iv) real-time tumor-tracking, in which radiation beams are continuously adapted in order to follow the tumor's changing position (22). RGRT was implemented at the VU University Medical Center in 2005 and is a specific focus of this thesis.



**Figure 1.** Image-guided radiotherapy (IGRT) for locally-advanced lung cancer; outline of the thesis.

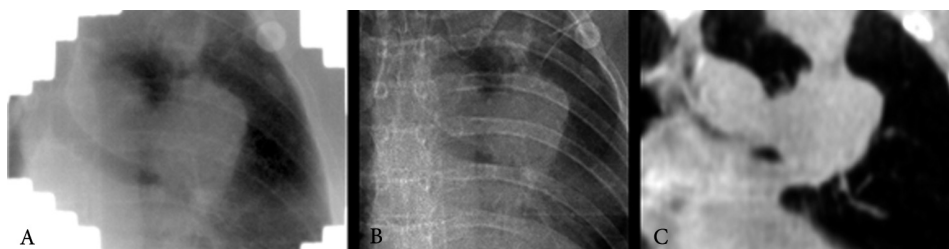
## Treatment verification

Despite the use of tailored margins for radiotherapy planning, and improved treatment planning and delivery approaches, a risk of geometric uncertainty related to the use of smaller treatment fields remains. In addition, knowledge of changes in tumor volume and position during a course of radiotherapy, referred to as ‘time trends’, is still limited. It is important that these uncertainties are well documented in order to stimulate the development of more accurate imaging techniques for verifying radiation delivery, both during a treatment fraction and course.

## IMAGE-GUIDED RADIOTHERAPY (IGRT)

Radiotherapy is by definition image-guided, as it involves the integration of imaging modalities in every key aspect of the process (figure 1). Target definition is generally CT-based (3D or 4D), with or without functional imaging such as  $^{18}\text{F}$ FDG-PET. Image-guided radiotherapy (IGRT) with respect to treatment verification refers to the process of repeat imaging in the treatment room in order to allow treatment decisions to be made on the basis of these images (23). The specific goal of IGRT in treatment verification is to increase accuracy during the actual delivery of radiation (intra-fraction) and between different fractions (inter-fraction). Planar mega-voltage (MV) imaging from 2 orthogonal directions using an electronic portal imaging device (EPID) and on-board imagers using kilo-voltage (kV) X-rays are generally used to verify setup during treatment (figure 2). Although improvement of setup inaccuracies is an important aspect of radiotherapy, this will only be addressed to a limited extent in this thesis (Chapter 5). Planar MV- and kV-imaging techniques are generally suboptimal for visualizing soft-tissues (tumors) during treatment due to the lack of contrast. Tumor visualization requires the implantation of radiographic markers, or the use of surrogates of tumor position such as the respiratory waveform or carina. Improved volumetric imaging is possible using in-room CT imaging (cone-beam CT; CBCT) and both kV and MV beams have been used for this purpose (figure 2) (24-26). A CBCT can be co-registered with the planning CT scan on both bony anatomy and soft tissues, allowing for the verification of setup, internal anatomy

and dosimetric profiles. Yet pre-fractional imaging, as mentioned above, does not allow for real-time evaluation of the tumor position. Approaches to provide intra-fractional information of the internal anatomy include time-integrated electronic portal imaging (TI-EPI) and MV-cine (27,28).



**Figure 2.** (A) anterior-posterior (AP) mega-voltage image, (B) AP kilo-voltage image (kV), and (C) frontal view of a kV cone beam CT of the same patient

## OUTLINE OF THE THESIS

IGRT plays a pivotal role in the treatment of lung cancer and this thesis describes the optimization of IGRT with respect to the key aspects of the treatment chain (Fig. 1.). In Chapter 2 recent developments in image-guided approaches regarding target definition, treatment planning and delivery are reviewed. The cornerstone of IGRT is an accurate and reproducible target definition, but consensus on defining target volumes is lacking for a number of clinical indications. In Chapter 3, the routine target volumes used by international experts for post-operative adjuvant radiotherapy are analyzed, both before and after use of a contouring protocol developed for a prospective study, Lung Adjuvant Radiotherapy Trial (Lung ART). Respiratory-gated radiotherapy (RGRT) is a relatively new treatment approach developed in an attempt to reduce toxicity by permitting the use of smaller treatment fields. RGRT is triggered by an external surrogate, i.e. abdominal respiratory motion, and requires a reproducible breathing pattern throughout treatment. The impact of changes in respiration on lung tumor position is evaluated in Chapter 4. Since the relationship between external surrogates and the internal anatomy may

be inconsistent, reproducibility of the internal anatomy during RGRT is studied in Chapter 5. External surrogates have been used to trigger RGRT, as lung tumors are often difficult to visualize using planar MV and kV imaging techniques. However, internal surrogates may be more reliable in verifying tumor position. In Chapter 6 two internal surrogates are evaluated regarding their ability to predict 3D tumor position. RGRT permits the use of smaller radiation fields, but may result in a geometric miss when changes in tumor, surrounding tissues or patient anatomy occur during treatment. The dosimetric consequences of these changes in patients treated with concurrent chemo-radiotherapy are evaluated in Chapter 7. A subgroup of patients undergoing image-guided concurrent chemoradiotherapy showing down-staging after 46 Gy may benefit from surgery. Since the split period related to re-staging may negatively influence outcomes in those not suitable for surgery (thus continuing radiotherapy), a strategy to limit the duration of the split period is described in chapter 8.



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